Synthesis and function of gut-associated lymphoid-tissue-resident *Alcaligenes faecalis* lipooligosaccharide partial structures

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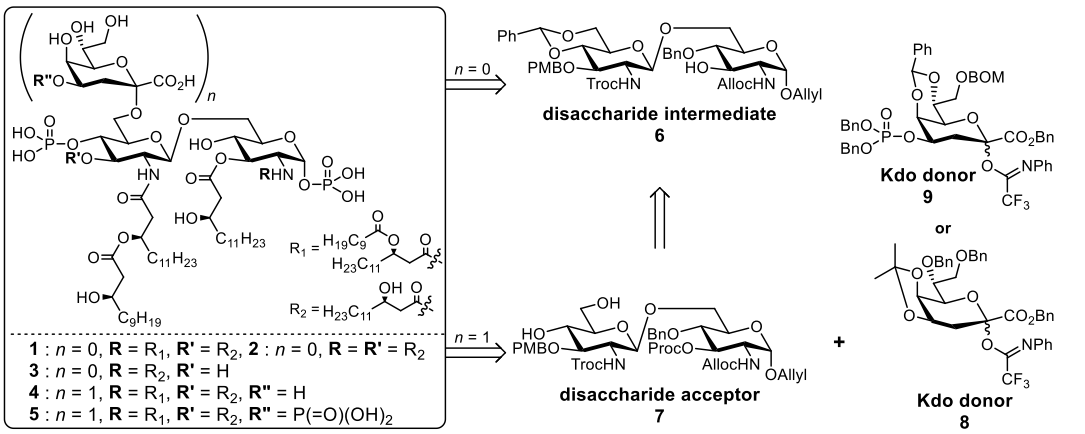
Alcaligenes faecalis is a Gram-negative bacterium inhabiting the gut-associated lymphoid-tissue, such as Peyer's patches. We previously reported that lipooligosaccharide (LOS) extracted from *A. faecalis* showed efficient antibody production effect without triggering any harmful responses[1], thus *A. faecalis* LOS and its active center lipid A are expected to be applied as a vaccine adjuvant.

We recently characterized the chemical structure of *A. faecalis* LOS and synthesized its lipid A moiety **1-3** via disaccharide intermediate **6**[2]. *A. faecalis* LOS and synthesized lipid A **1** showed the TLR4-dependent immunostimulating activities, while synthesized *A. faecalis* lipid A **2, 3**, which were the main components in *A. faecalis* LOS, worked as TLR4 antagonists. Thus, there was a functional divergence between the main component lipid As and LOS. On the other hand, we previously found that the Kdo linking lipid A and core oligosaccharide affect the immune function of lipid A[3].

In this study, to investigate how Kdo impacts the immune function of *A. faecalis* lipid A, we synthesized *A. faecalis* Kdo-lipid A **4, 5**. After glycosylation of **7** with Kdo donor **8**[4] whose sugar backbone was fixed in a boat-like conformation to enhance the α-selectivity of glycosylation, selective removal of protective groups and sequential introduction of fatty acids afforded *A. faecalis* Kdo-lipid A **4**. In a similar strategy to the synthesis of **4**, we also synthesized **5** from **7** and Kdo donor **9**. Bioassay using HEK-Blue™ hTLR4 indicated that Kdo-lipid A **4** showed slightly stronger immunostimulating activity than lipid A **1**.



(1) *Mucosal Immunology* **2018**, *11*, 693. (2) *Angew. Chem. Int. Ed.* **2021**, *60*, 10023. (3) *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1475. (4) *SYNLETT* **2011**, *16*, 2359.